Amendments to the Claims

This listing of claims will replace all prior versions, and listing, of claims in the application.

Listing of Claims

1. (currently amended): A compound of formula (I):

$$\begin{array}{c|c}
R^2 & R^1 \\
\hline
N & R^3 & R^4
\end{array}$$
(I)

wherein

 R^1 is <u>n-propyl, 1-methylethyl, 2-methylpropyl, or 3,3-dimethylpropyl</u> C_1 - C_6 -alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1 - C_3 alkyl), -O-(C_1 - C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3 - C_6 cycloalkyl), -SO₂-(C_1 - C_3 alkyl),

-CN, -COO-(C₁-C₂ alkyl) and -OH); C₂-C₆ alkenyl; (CH₂)_q-Ar₂; or a group of formula (i) or (ii)

$$(CH_2)_{\mathsf{r}} \overset{\mathsf{Z}}{\underset{(CR^7R^8)_{\mathsf{t}}-\mathsf{X}}{\mathsf{X}}} \overset{(CH_2)_{\mathsf{r}}}{\underset{(CR^7R^8)_{\mathsf{t}}-\mathsf{X}}{\mathsf{X}}} \overset{(CH_2)_{\mathsf{r}}}{\underset{(CR^7R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CH_2)_{\mathsf{r}}}{\underset{(CR^7R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CH_2)_{\mathsf{r}}}{\underset{(CR^7R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CH_2)_{\mathsf{r}}}{\underset{(CR^7R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\mathsf{X}}} \overset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\underset{(CR^8R^8)_{\mathsf{r}}-\mathsf{X}}{\overset$$

R², R³ and R⁴ are each independently selected from hydrogen or C₁-C₂ alkyl;

 R^5 , R^6 , R^7 and R^8 are each independently selected from hydrogen or C_1 - C_2 alkyl;

-X- is a bond, -CH₂-, -CH=CH-, -O-, -S-, or -SO₂-;

-Y- is a bond, -CH₂- or -O-;

-Z is hydrogen, –OH or -O-(C₁-C₃ alkyl);

p is 0, 1 or 2;

q is 0, 1 or 2;

r is 0 or 1;

s is 0, 1, 2 or 3;

t is 0, 1, 2, 3 or 4; and

Ar_1 is selected from:

- (i) a phenyl group or a 5 or 6 membered monocyclic heteroaromatic group each of which is optionally substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C₁-C₄ alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridinyl, pyrazolyl, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents; pyridinyl; or pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C₁-C₄ alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents 1, 2, 3, 4 or 5 substituents (depending on the number of available substitution positions) each independently selected from halo, eyano, C₁-C₄alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridinyl, pyrazolyl, phenyl (optionally substituted with 1, 2 or 3 halo substituents), benzyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents) with the proviso that only C₁-C₄alkyl may be a substituent for the H of any -NH- moiety present within a 5- or 6-membered monocyclic heteroaromatic group; or
- (ii) a naphthyl group or an 8, 9 or 10 membered bicyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C₁-C₄alkyl (optionally substituted with 1, 2 or 3 F atoms), -O (C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S (C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C₁-C₄alkyl may be a substituent for the H of any NH- moiety present within an 8 , 9- or 10-membered bicyclic heteroaromatic group; and

Ar₂ is selected from

(i) a phenyl group or a 5- or 6-membered monocyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4 or 5 substituents (depending

on the number of available substitution positions) each independently selected from halo, cyano, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C_1 - C_4 alkyl may be a substituent for the H of any -NH- moiety present within a 5- or 6-membered monocyclic heteroaromatic group; or

(ii) a naphthyl group or an 8-, 9- or 10-membered bicyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C₁-C₄alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C₁-C₄alkyl may be a substituent for the H of any -NH- moiety present within an 8-, 9- or 10-membered bicyclic heteroaromatic group;

or a pharmaceutically acceptable salt thereof; provided that:

- (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms;
- (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms;
- (c) when -Z is -OH or $-O-(C_1-C_3$ alkyl), then -X- is $-CH_2$ -;
- (d) when -Y- is -O- then p cannot be 0; and
- (e) the compound 3 [(phenylmethyl) (3S) 3 pyrrolidinylamino] propanenitrile is excluded.
- 2. (currently amended): The A compound according to claim 1, wherein Ar_{+} is phenyl pyridinyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridinyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_{+} - C_{+} alkyl (optionally substituted with 1, 2 or 3 F atoms) and -S- $(C_{+}$ - C_{+} alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridinyl, pyrazolyl, phenyl (optionally substituted with 1, 2 or 3 halo substituents); and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and

wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C₁-C₄ alkyl (optionally substituted with 1, 2 or 3 F atoms), O (C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms), and S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms); and

Ar₂ is naphthyl, pyridinyl, thiazolyl, furanyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridinyl, thiazolyl, furanyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms).

3. (currently amended): The A compound according to claim 1, wherein R¹ is n-propyl, 1-methylethyl, 2-methylpropyl, or 3,3-dimethylpropyl C₄-C₆ alkyl, C₂-C₆ alkenyl, -(CH₂)_m-CF₃, -(CH₂)_n-S-(C₁-C₃ alkyl), -(C₁-C₃ alkyl), -(C₁-C₅ alkylene)-O-(C₁-C₃ alkyl), -(C₁-C₅ alkylene)-O-(C₃-C₆ cycloalkyl), -(C₁-C₅ alkylene)-SO₂-(C₁-C₃ alkyl), -(C₁-C₅ alkylene)-OCF₃, -(C₁-C₆ alkylene)-OH, -(C₁-C₅ alkylene)-CN, -(CH₂)_q-Ar₂ or a group of formula (ia), (ib) or (ii)

$$(CH_2)_r$$
 $(CR^5R^6)_s$
 $(CH_2)_r$
 $(CH_2)_p$
 (CH_2)

 R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , -X-, -Y-, p, q, r and s are as defined in claim 1; m is 1, 2 or 3;

n is 1, 2 or 3;

t is 2, 3 or 4; and

-Ar₁ is <u>as defined in claim 1 phenyl, pyridinyl, thiazolyl or naphthyl; wherein said phenyl, pyridinyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C₁-C₄ alkyl, O-(C₁-C₄ alkyl), O-(C₁-C₄ trifluoroalkyl), S-(C₁-C₄ alkyl), S-(C₁-C₂ trifluoroalkyl) and/or with 1 substituent selected from pyridinyl, pyrazolyl, phenyl</u>

(optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C₁-C₄ alkyl, -O (C₁-C₄ alkyl), -O (C₁-C₄ difluoroalkyl), -O (C₁-C₄ trifluoroalkyl), -S (C₁-C₄ alkyl), -S (C₁-C₂ trifluoroalkyl); Ar₂ is naphthyl, pyridinyl, thiazolyl, furanyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C₁-C₄ alkyl, trifluoromethyl and -O-(C₁-C₄ alkyl).

- 4. (currently amended): The A compound of claim 1, wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are each hydrogen.
 - 5. (canceled)
 - 6. (canceled)
 - 7. (canceled)
 - 8. (canceled)
 - 9. (canceled)
- 10. (currently amended): The A compound of claim 1, wherein R^1 is -(C₄-C₅ alkylene)-OH.
- 11. (currently amended): <u>The A compound of claim 1</u>, wherein R¹ is a group of formula (i), r is 0, s is 2, t is 2, -Z is hydrogen and -X- is -O-, -S- or -SO₂-.
 - 12. (canceled)

- 13. (currently amended): The A compound of claim 1, wherein R^1 is a group of formula (i), r is 0, s is 1, 2 or 3, t is 1, -Z is hydrogen and -X- is -CH₂-.
- 14. (currently amended): <u>The A compound of claim 1</u>, wherein R¹ is a group of formula (i), r is 1, s is 0, 1, 2 or 3, t is 1, -Z is hydrogen and -X- is -CH₂-.
 - 15. (canceled)
- 16. (currently amended): The A compound of claim 1, wherein R^1 is $-(CH_2)_q$ -Ar₂, and q is 1.
- 17. (currently amended): The A compound according to claim 16, wherein -Ar₂ is pyridinyl, phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl or C_1 - C_4 alkyl.
 - 18. (cancelled).
- 19. (currently amended): The A compound of claim 1, wherein $-Ar_1$ is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1 - C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridinyl, pyrazolyl, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents.
 - 20. (canceled)
 - 21. (canceled)
 - 22. (canceled).
 - 23. (canceled)
- 24. (previously presented): A pharmaceutical composition, comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, or

3-[(phenylmethyl)-(3S)-3-pyrrolidinylamino]-propanenitrile or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier. 25. (canceled) 26. (canceled) 27. (canceled) 28. (canceled) 29. (previously presented): A method for treating attention-deficit hyperactivity disorder (ADHD), comprising administering to a patient in need thereof an effective amount of a compound of claim 1 which selectively inhibits the reuptake of norepinephrine over serotonin and dopamine, or a pharmaceutically acceptable salt thereof. 30. (canceled) 31. (canceled) 32. (canceled) 33. (canceled) 34. (canceled) 35. (canceled) 36. (canceled)

Remarks

It is respectfully submitted that Claims 1-4, 8, 10-11, 13-14, 16-19, 22, 24, and 27-29 are pending, as Claims 5-7, 9, 12, 15, 20, 21, 23, 25-26, and 30-36 were cancelled in the Preliminary Amendment submitted November 29, 2005 (See File History). Regarding the present response to the Examiner's Office Action dated May 2, 2008, Claims 8, 18, 22, 27-28 have been canceled. In an effort to advance prosecution, Claims 1-3 have been amended in view of applicants' election of Group I, and thus are limited to compounds wherein Ar₁ is phenyl which is optionally substituted. Specifically, Applicants have amended Claim 1 to include the definition of phenyl optionally substituted from Claim 18 in Claim 1. Basis for these amendments can be found in the specification at least on page 16, line 4 through page 17, line 2. Applicants have further limited the scope of Claim 1 to include only those compounds where R¹ is n-propyl, 1-methylethyl, 2-methylpropyl, or 3,3-dimethylpropyl. Basis for this amendment can be found in the specification at least on page 14, lines 6-7. Applicants also assert that this amendment brings the below pictured compound, an intermediate disclosed in J. Med. Chem. 1999, 42, 677-690 as an intermediate in the synthesis of 3-[2-(pyrrolidine-1-yl)ethyl] indoles provided to the office in form 1449 on November 29, 2005 (See File History) outside the scope of Claim 1.

In addition, Applicants have made minor typographical amendments to Claims 2-4, 10-11, 13-14, 16 and 17. Applicants have also removed redundant language from Claims 2 and 3. Remarks below further address the above-referenced Office Action.

Election/Restrictions

The Examiner has asserted that the present application contains multiple inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1, and thus has required applicants to elect a single invention to which the claims must be restricted.